REMARKS

Claims 1-2, 4, 6, 9-11, 13-23, 25, 27, 30-39 and 44-46 are active. Claims 3, 5, 7-8, 12, 24, 26, 28-29, and 40-43 are canceled. Claim 1 is rejected under 35 USC 112, second paragraph. Claim 4 is objected to. Claims 1, 2, 4, 6, 9-11, 13-18, 27 and 46 are rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432 in view of Wolfinbarger '104. Claims 25, 30-32, 44 and 46 are rejected under 35 USC 102 as anticipated by Wolfinbarger '432. Claim 27 is rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432. Claims 33, 36, 37, and 39 are rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432 in view of Morris WO 01/58497. Claims 34 and 35 are rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432 in view of Wolfinbarger '970. Claims 38 and 46 are rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432 in view of Morris. Claim 45 is rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432 in view of Peterson '933.

Amendment is made to claim 1 to meet the rejection based on 35 USC 112. Claim 4 is amended to meet the objection thereto. These bases of the rejection are believed met and should be withdrawn.

Amended claims 1-2, 4, 6, 9-11, and 13-23 and claims 25, 27, 30-39 and 44-46 are presented for the Examiner's reconsideration.

Claim 1

This claim is rejected under 35 USC 103 as being unpatentable over Wolfinbarger '432 in view of Wolfinbarger '104. Applicants traverse this conclusion.

Claim 1 calls for:

> centrifuging the tissue in a centrifuge with a flowing pathogen solvent reducing solution wherein the solution is flowed continuously to and away from the centrifuge containing the tissue during the centrifuging, the centrifuge producing a G force on the material to remove material from the tissue and promote penetration into the tissue
>
> the centrifuging causing penetration of the pathogen reducing solution into substantially all of the cavities of the tissue where the pathogens reside to thereby inactivate and/or reduce the pathogen content in said cavities

The Action cites '432 as teaching centrifuging a tissue with a pathogen solvent. After treatment, the Action states the bone is dry spun citing col. 13, lines 46-48. The reference does not expressly state this in so many words, the Action implicitly deriving dry spinning from the reference's silence to this issue. The Action states that the reference discloses that "if the amount of lipid material to be solubilized exceeds the solubilization capability of the detergent present, lipid solubilization will not be complete." Then the Action states that "To this effect, Wolfinbarger, Jr. et al. suggests that by 'continually changing the detergent solution over time, it becomes possible to completely solubilize all solubilizable lipid present in the bone Graft.' "

This statement cited by the Action is to the fact that solubilization of a lipid with a detergent is disclosed and that '432 is interested in removing the bone marrow which harbors pathogens, viruses and so on. Col. 4, lines 39-47. But solubilization is concerned with making the otherwise insoluable lipids soluable in a solution to remove the lipids. This does not inactivate all pathogens as discussed in '432. It is the detergent which performs solubilization, but other materials are required for complete inactivation and removal of all pathogens.

The detergent also has certain antibacterial and/or antiviral effects. However, at col. 8, lines 11-22, the reference states it is possible to add strong viral/bacterial inactivators to a disposable collection container to further inactivate potential pathogenic and/or biohazardous biomaterials. Therefore the reference contemplates that the precleaning and cleaning processes, with a detergent, may not be sufficient to remove all biohazardous biomaterials from the bone.

The '432 reference also discusses traditional flushing procedures to remove bone marrow as being a hazard to processing personnel. Col. 8, lines 23-29. Col. 8 line 40 et seq. discusses precleaning and cleaning with a detergent solution and may include an antibiotic, an antiviral agent, and other agents and strong acids. Col. 9, lines 18-17. See also lines 45-48 for further discussion on this subject matter. Washing solution is also discussed at col. 9, lines 49 et seq. It appears that the '432 reference intends all of these cleaning processes to occur outside of and prior to the centrifuge and that detergent alone is not sufficient.

In view of the above, in regard to the various cleansing processes employed in '432, it is not seen that there is a suggestion in '432 to flow a solution continuously to and away from the centrifuge containing the tissue during the centrifuging in the manner claimed in view of '432 thereby causing penetration of the pathogen reducing solution into substantially all of the cavities of the tissue where the pathogens reside to thereby inactivate and/or reduce the pathogen content in said cavities. Pre-cleaning with a detergent or other substances prior to centrifuging is not the same.

The Action cites '104 which discloses another method of bone treatment with the continual replacement of solvent wherein the solvent solution is flowed continuously to and away from the treatment chamber. The Action concludes that it would have been obvious to provide a means to continuously introduce to and remove solvent from the centrifuge of '432 to completely solubililze all solubilizable lipids for reasons cited by '432 and '104. However, solubilization is a technique to dissolve the lipids that harbor the pathogens, but is not the final process needed to remove all pathogens as discussed above.

As discussed in '432, solubilization per se of the lipids does not remove all pathogens. This conclusion of obviousness does not follow from the teachings of these two references which, except for applicants' disclosure, are otherwise unrelated.

As to '432, col. 8, lines 5-10, the Action states:

> that the reference discloses that "if the amount of lipid material to be solubilized exceeds the solubilization capability of the detergent present, lipid solubilization will not be complete." "To this effect, Wolfinbarger, Jr. et al. suggests that by 'continually changing the detergent solution over time, it becomes possible to completely solubilize all solubilizable lipid present in the bone Graft.' "

These statements are taken out of context of the '432 disclosure. These statements are found in the section of '432 entitled "A. General Process" at col. 7, line 43. This section states in the paragraph starting at line 44, col. 7, "The present process includes the step of centrifuging a cut bone graft." lines 44-45. It then states

> "Prior to and/or after the first centrifuging, the bone grafts may optionally be incubated in one or more pre-cleaning solutions, cleaning solutions and/or washing solutions. After a particular incubation, the

bone grafts may **optionally** be centrifuged." (emphasis and underlining added)

Plainly, this section states that the pre cleaning, cleaning and/or washing steps occur by incubation and not during centrifuging. Centrifuging occurs after and/or prior to the incubation. Thus this section teaches that to clean the tissue the cleaning comes first during an incubation step. This incubation step is prior (or after) to any centrifuging. This is expressly disclosed.

At col. 7, lines 57-61, '432 also states

"The steps of pre-cleaning, cleaning and incubating can include one or more of: lavaging, soaking, sonicating and agitating the cut bone grafts. Agitation can be performed using, for example, a gyrating shaker and/or a paint can shaker."

None of the above noted steps are disclosed as being implemented in a centrifuge. A washing step (lavaging), soaking step, sonicating step and agitating step are not steps that one of ordinary skill would implement in a centrifuge; these are separate steps contemplated by '432 as occurring prior to any centrifuge step as expressly disclosed. The disclosure of '432 thus teaches away from using a centrifuge employing the flowing of a solvent continuously during the centrifuging as claimed, which teaching away is the antithesis of obviousness.

The next paragraph at col. 7 starting at line 62 discusses detergents. It is in this paragraph that the Office Action makes the statement

"if the amount of lipid material to be solubilized exceeds the solubilization capability of the detergent present, lipid solubilization will

> not be complete." "To this effect, Wolfinbarger, Jr. et al. suggests that by 'continually changing the detergent solution over time, it becomes possible to completely solubilize all solubilizable lipid present in the bone Graft.' "

Taken in the context as contemplated by '432 in view of the above prior discussion starting at col. 7, line 44 to line 67, it is expressly the intention of this disclosure that the detergent which is used for precleaning or cleaning or the lavaging or soaking or during sonicating or during agitating that these processes are batch processes wherein the graft is placed in the cleaning media in a non-centrifuging operation and cleaned. The quoted statement in the Action taken at col. 8, lines 5-10, overlooks the context expressed by '432 at col. 7, line 67 to col. 8, line 1-4.

Here it is stated that the formation of micellar structures tends to limit the effective concentration range for detergent solutions. Thus soaking of bone in a given volume of detergent solution may not be totally effective in that the absolute amount of detergent present is limited and if the amount of lipid material to be solubilized exceeds the solubilization capability of the detergent present, the lipid solubilization will not be complete. In this case, '432 suggests to continually change the detergent solution over time. This latter statement taken out of context by the Action means that if the soaking, lavaging etc of the graft in a detergent is such that the detergent is not effective to completely solubilize the lipids, then repeat the process by changing the detergent solution.

What this section is stating is that before centrifuging, if the lipids are not solubilized fully at first, repetitively change the detergent until the solubilization is complete. But the important aspect of this section is that all of

this cleaning mode occurs prior to centrifuging. The only time that the cleaning detergent needs to be changed is only in that instant that the involved lipids exceed the detergent capability to solubilize the lipids in a batch cleaning process. This is all that one of ordinary skill is taught by this section of '432. Any other conclusion is not based on this reference, but using applicants' disclosure as a guide, which is proscribed hindsight.

The entire section of '432 at col. 7, line 44 to col. 8, line 10, is directed to cleaning the graft with lavaging, soaking, sonicating and agitating only in a batch process and if the detergent involved is insufficient due to the volume of the batch process, then replace the detergent as needed. This reference does not suggest applying a cleaning solution during centrifuging. The reference does not go so far and such a conclusion does not logically follow from the '432 disclosure. Col. 8, line 11 expressly states that centrifuging involves induced flow of a solvent and disavows the use of pressurized flushing procedures, col. 8, lines 23-29, as being hazardous to personnel.

The entire section including cols. 9 – 12 is concerned with cleaning solutions in batch operations. See col. 11, line 19-20 stating that the bone is immersed in the subsequent solution in the container. Obviously emmersion in a container is a batch process and not involved with continuous centrifuging. At col. 11, line 67 – col. 12, lines 1-4, '432 states the grafts are rinsed with sterile water (line 1, col. 12) and placed in a sterile can (line 4), placed in a basin (line 13). It is only afterwards, that the grafts are placed in a hydrogen peroxide solution in a centrifuge (lines 20 et seq.) This latter step does not suggest what is claimed. Thus, there is a very lengthy discussion in '432 about the importance of batch precleaning. This again teaches away

from the continuously flowing of claim 1 of a solvent which contradicts the conclusion of the Action.

Of course flowing the solution during centrifuging is advantageous and possible, but that is what applicants teach, and not '432. This reference does not suggest what is claimed. It is only concerned with batch processing and certainly not continuously flowing a solvent during and while centrifuging. The application of detergent in the so called continuous process is prior to or after centrifuging and not during. To conclude otherwise is an improper extension of '432.

The Action implies that '432 suggests applying the detergent in a continuous process during centrifuging. As pointed out in detail above, this is not what '432 expressly discloses or suggests. The continuous changing of detergent is not during centrifuging, but prior to centrifuging. To read into this disclosure that continually changing the detergent means doing so during centrifuging is misreading the previous and subsequent lengthy discussion of this section of '432 which states that the detergent is only applied in the stated processes prior to centrifuging. Therefore, the term "continually changing the detergent solution over time" does not mean at any time, but only in that time during which the cleaning is normally conducted.

To this end, the Action cites '104 as teaching a continuous process for replacing a solvent. But this process taken in conjunction with '432 at best only can mean to perform this continuous process before centrifuging as expressly disclosed by '432. '104 does not disclose its process as occurring during centrifuging. '104 discloses a pressurize system wherein a hole 2 is drilled in the femur bone 1, the hole being tapped at 3, Fig. 1. A solvent line 4

is then attached to the tapping port 3. The bone is placed in a sterile container 5.

The line 4 and bone 1 of '104 are not shown being capable of being operated on with this cleaning process in a centrifuge nor is a centrifuge discussed or disclosed in this reference for use with this apparatus. '104 does not disclose its process as being useful in a centrifuge. Neither '432 nor '104 suggest any such precleaning should occur during centrifuging. There is no motivation to one of ordinary skill to want to use a continuous cleaning process such as disclosed in '104 in a centrifuge of the type disclosed in '432. No such suggestion is found in either reference. No convincing line of reasoning is given as to from what disclosure one of ordinary skill is provided motivation to do what is claimed.

The Action states the advantage is to completely solubilize all solubilizable lipids. But what is ignored is that '432 does this outside of the centrifuge and no advantage is expressed as to why one of ordinary skill would want to use a centrifuge as compared to the '432 disclosed process to solubilize the lipids per se. '432 discloses at col. 11, line 60 further embodiments. These embodiments also refer to batch cleaning or centrifuging with a solvent, but no continuous flow of inactivation solvent is disclosed as claimed. At col. 12, line 4, a can is used, and at lines 13 and 28, a basin is used. But no continuous flow with the centrifuging disclosed. See col. 12, lines 20 et seq.

There is no suggestion of a problem with using conventional centrifuges without such cleaning on a continuous basis as claimed nor is there any disclosure as to any advantage to do so as claimed. That is

applicants' contribution and not that of the references. It is believed that claim 1 is allowable.

Claim 25

This claim is rejected over '432 and calls for:

> centrifuging the tissue with a pathogen solvent reducing solution to produce a G force on the tissue in a direction parallel to the bone longitudinal axis

Exhs. 1 and 2 attached are each copies of the ref. '432 patent figures 1 and 5 marked in red ink for purposes of this response. The Action states that '432 discloses centrifuging will produce a G force on the graft in a direction parallel to the longitudinal axis of the graft 13 citing col. 4, lines 21-34. Applicants have carefully reviewed this section and all of '432, but fail to find support for this conclusion. This section of '432 merely refers to centrifuging. Fig. 5 shows a graft 13, which the Action states has a longitudinal axis. This may be true. But '432 does not define which direction the G forces are exerted on the graft or what orientation the graft is placed in with respect to the axis of rotation of the centrifuge which axis is not disclosed.

Col 7 line 44 et seq also refer to centrifuging. Again the orientation of the bone that is centrifuged with respect to the direction (orientation) of the applied G forces is not disclosed. Claim 25 requires the G forces to be parallel to the longitudinal axis of the bone. That is, the bone has a specific orientation with respect to the axis of rotation of the centrifuge. All that is disclosed is mere possibilities of such relative orientations. No specific example is provided. It is not understood on what basis there is support in '432 that the Action is referring to when it refers to the direction of the G forces as being

parallel to the bone longitudinal axis in '432 other than it might be a possibility to so orient the two axes. But mere possibilities is insufficient to provide an anticipation of what is claimed..

The cited section of '432 does not, nor does the remainder of the '432 disclosure, provide such support. Figs. 1 and 5 do not show the axis of rotation of the centrifuge. One graft 13, an iliac crest wedge, is shown in Fig. 5 and a femur 11 is shown in Fig. 4. The femur of Fig. 4 is attached to the holding device 5 with its long axis vertical as compared to the long axis A, Exh. 1, of the wedge Fig. 5. Exhibit 1 is reproductions of the reference '432 patent Figs. 1 and 5. The red arrow in Fig. 5 labeled G is the Action assumed possible direction of the G forces out of infinite possible directions, if the device 2 of Fig. 1 were to be rotated about the assumed one possible x axis shown in red ink out of an infinite number of possible x axis directions.

However, the x axis is not described in the '432 patent, but is shown in this orientation only for purposes of this response and appears to be the assumed direction in the Action. The relative angle of orientation of the graft to the angle of orientation of the axis of rotation (x in Exh. 1 or y in Exh, 2, for example in this case) of the holding device is not disclosed in '432. The Office Action assumes that the axis of rotation is at the x axis of Exh. 1. But this orientation of the x axis has no express support in this reference. Also the Action assumes that the orientation of the graft 13 in Fig. 5 of '432 is such that its long axis A is oriented parallel to the G force arrow G. But this assumption has no express support and is also only one of numerous possibilities. These assumptions are only mere one of numerous possibilities.

The graft long axis A may be oriented in the perpendicular direction of axis B (in red ink) or any other possible angular orientation not specified. This is because no express relative orientation of the graft relative to the axis of rotation of the centrifuge is disclosed as having any significance. The Action's correspondence of the graft longitudinal axis to the G force axis as parallel is only an unsupported assumption.

To support anticipation, the asserted orientation of the graft to the axis of rotation of the centrifuge must always occur as shown in Exh. 1. Obviously such an orientation relationship is only one of numerous possibilities. To be anticipating, means that these relative orientations always occurs and is not a mere possibility. For example, Exh. 2 shows an orientation of the centrifuge axis of rotation y as being inclined to the orientation of axis x of Exh. 1. At this inclined axis of rotation, the G force direction will be inclined to the graft longitudinal axis and not parallel as claimed.

As a further example that the '432 patent does not consider the relative orientation of the bone longitudinal axis to be significant,. refer to Fig. 4. Here the femur 11 has a head which is elliptical and a shank that defines a longitudinal axis that is vertical in the Fig. and parallel to the x axis of Exh. 1. In this case, if the femur is rotated about the x axis, its longitudinal axis, vertical in this case, would not be parallel to, but normal to, the G force direction.

There is no support in this reference as to any corresponding orientation of the graft longitudinal axis to the normal direction, the direction of the G force, of the centrifuge axis of rotation. Fig. 5 is only a sketch of the relationship of the graft orientation to the holder and much less an express

disclosure of a possible axis of rotation of the holder not disclosed. The graft may have any axial orientation to the axis of non disclosed rotation of the centrifuge.

With respect to anticipation and inherent disclosure, the referred to disclosure of a reference must always occur and not be mere possibilities to be inherent. See MPEP 2163.07(a). See also the cited case *In re Robertson*, 49 USPQ 1949 (CAFC 1999), where the board was reversed on the issue of anticipation by inherence. The court states "Board's analysis rest upon the very kind of probability or possibility-the odd use of fasteners with other than their mates –that this court has pointed out is insufficient to establish inheritance. "Inherence may not be established by probabilities and possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Finnigan Corp. v. ITC* 51 USPQ 2d 1001 (CAFC 1999).

Consequently, to support an anticipation of claim 25, '432 must necessarily disclose that the graft longitudinal axis is always oriented parallel to the G force direction. This is not true since the reference is silent as to these relationships. Claim 25 is not obvious in view of '432 much less anticipated thereby. This claim is believed allowable.

Claim 38

This claim calls for:

> A process for introduction of at least one growth factor in animal tissue comprising centrifuging the tissue in the presence of a liquid containing the at least one growth factor.

The claim is rejected under 35 USC 103 over '432 in view of Morris WO '497. '432 is cited as teaching centrifuging. Morris is cited as disclosing it was known in the art to impregnate a bone with a growth factor, citing page 1, first paragraph. What is disclosed is a pressure flow system. Two chamber sections 12 and 14 are disclosed which are combined with a hinge 18 to form an interior chamber 16 for receipt of pressurized fluids and portions of the work piece. The chambers have inlet and outlet ports and connect to vacuum or pressure sources. Other structures are also provide this system.

This is an entirely different system than a centrifuge and operates under different principles. There is no suggestion in this reference that the disclosed growth factor could or should be applied via a centrifuge. The Action concludes it would be obvious to impregnate the bone with a growth factor as claimed. However, this conclusion begs the issue. No motivation to do so is provided. There is no suggestion in Morris of impregnating the growth factor with a centrifuge or that this approach would be adequate to do so. While the pressure system of Morris and the claimed process might be functional equivalents, equivalency is not a test of obviousness.

See MPEP 2144.06 citing *In re Scott* and the discussion concerning this citation regarding equivalents. Things that are functional or mechanical equivalents are not necessarily obvious in view of one another. The fact that Morris discloses a pressure system for applying a growth factor is not a basis for a conclusion that centrifuging is equivalent thereto and thus obvious thereover. There is no teaching in Morris that centrifuging would or could impregnate the growth factor in a manner that would be effective. This is an

obvious to try conclusion and obvious to try is not a test of obviousness. *In re Scott.* This claim is believed allowable.

Claim 45 is rejected as obvious over '432 in view of Peterson '933. This claim calls for:

> A process for providing infusion of a radiation protectant into tissue having a plurality of cavities comprising centrifuging the tissue with a solution in a wet spin to produce a G force on the material to remove material from the tissue and promote solution penetration into the tissue, the centrifuging penetrating the radiation protectant into substantially all of the cavities of the tissue.

Peterson is cited as teaching it was known to use radiation to sterilize bone before use and to add a radiation protectant to the bone before irradiation thereof. The conclusion of the Action states that '432 teaches that the process of centrifuging is effective in moving fluids into and out of bone. This begs the issue. The issue is what in these references suggests that the radiation protectant can be can be added to bone by centrifuging rather than by some other process.

Peterson '933 is silent as to the actual method of applying the radiation protectant. Peterson states that in order to preserve the physiological activity of the biologically active compounds during radiation sterilization, it is necessary to incorporate the compounds into a protected mixture. This reference states that an allogenic bone graft may be present in the protected mixture in an amount of 50 to about 99 percent by weight and preferably about 80 top about 99 percent by weight. col. 4, lines 9-23. The protected mixture comprises a protein which is about 1 to about 10 percent by weight of the protected mixture. col. 4, lines 30-35.

The method of applying the protected mixture is not given by '933. The protected mixture must be cooled to inhibit denaturation of the biologically active compound. The mixture is cooled by flash freezing to about -70° C. Preferably the mixture is frozen so that it is substantially immobilized. col. 8, lines 52-58. Freezing the mixture is not conducive to application in a centrifuge. Thus it appears that the proposed mixture is not one that would be intended for such a use. Therefore, '933 does not disclose a protectant that is applicable for use in a centrifuge and teaches away from such use, the antithesis of obviousness.

To conclude this frozen mixture is to be applied by centrifuging is a proscribed obvious to try conclusion. See *In re Scott* noted above and the cited MPEP section on equivalency. There is no support in '432 that centrifuging is an effective process for the '933 disclosed protectant. as claimed. While the two processes of '933 and as claimed might be equivalents, equivalency is not a test of obviousness. This claim is believed allowable.

Claim 46 is believed allowable by reason of the fact that all of the referred to claims are believed allowable. The remaining claims depend from the independent claims and are believed allowable for at least the same reasons.

Since claims 1-2, 4, 6, 9-11, 13-23, 25, 27, 30-39 and 44-46 have been shown to be in proper form for allowance, such action is respectfully requested.

No fee is believed due for this paper. However, the Commissioner is authorized to charge deposit account 03 0678 for any fee that may be due and to credit this deposit account for any overpayments.

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